

Neurosteroids and Postpartum Depression: The Mechanism, Efficacy, and Approval of Brexanolone and Zurzuva

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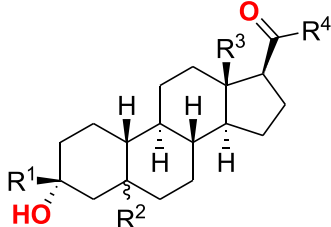
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ABSTRACT: Postpartum depression (PPD) affects 10–15% of new mothers globally. Marking a pivotal shift in treatment, the U.S. Food and Drug Administration approved Zurzuva (zuranolone) as the first oral medication for PPD in adults. This major depressive episode can emerge after childbirth or in pregnancy's later stages. Previously, PPD treatments were restricted to IV injections administered in select healthcare facilities. Childbirth instigates hormonal, physiological, and emotional shifts, with a stark drop in mood-regulating hormones like estrogen and progesterone possibly triggering depression. The role of serotonin in PPD is undeniable. Psychosocial stressors, such as neonatal care burdens and societal pressures, further amplify the risk. This Patent Highlight underscores the introduction of zuranolone as a beacon of hope for an effective and accessible treatment, which may benefit many postnatal women worldwide.

Important Compound Classes.



Titles. 3,3-Disubstituted 19-nor Pregnane Compounds, Compositions, and Uses Thereof; 19-Nor C3,3-Disubstituted C21-N-Pyrazolyl Steroid and Methods of Use Thereof; and Neuroactive Steroids and Their Methods of Use

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Disease Area. Postpartum depression

Biological Target. GABA receptor

Summary. Postpartum depression (PPD) poses a significant psychiatric challenge, affecting around 10–15% of new mothers globally. Instead of experiencing a joyful time after childbirth, many women find themselves battling this mood disorder. Though childbirth is biologically routine, it brings significant hormonal, physiological, and emotional changes. PPD arises from a combination of different factors, such as

- 1 Hormonal Dynamics:** After giving birth, mood-regulating hormones such as estrogen and progesterone drop sharply. This sudden shift can trigger depressive symptoms in susceptible women.
- 2 Neurotransmitter Interactions:** Serotonin, commonly called the “happiness chemical”, is essential for mood balance. Changes in its levels and activity after childbirth can contribute to PPD.
- 3 Psychosocial Triggers:** Apart from biological changes, various psychosocial stressors, including the demands of newborn care, chronic sleep deprivation, societal pressures, and self-image issues, can push a mother into depression. In the U.S., around 13% of postnatal women struggle with PPD. This rate is comparable to medical concerns like preterm births and gestational diabetes, highlighting the critical need to address PPD.

Neurosteroids and Their Role in Brain Function. Neurosteroids, like allopregnanolone (AP), play a crucial role in



modulating brain activities by regulating neuronal excitability and guiding network functions. They primarily work by allosteric regulating γ -aminobutyric acid A (GABA_A) receptors, vital for neural inhibitory processes. Neurosteroids can be categorized into pregnanes, androstanes, and sulfated derivatives. While pregnanes and androstanes enhance GABA_A receptor functions, sulfated derivatives often have opposite effects.

The brain, our body's most complex organ, functions through a delicate balance of neurotransmitters and their receptors. GABA is fundamental in this balance, managing neuronal activity throughout the central nervous system. Any disruption in GABA responses can lead to various neurological conditions, including depression.

Endogenous neuroactive steroids, such as AP, influence GABA receptors by enhancing their inhibitory functions. However, changes in these steroids after childbirth, significantly decreasing AP, might be behind PPD's development.

Brexanolone. The FDA's 2019 approval of brexanolone (BX) added a new dimension to PPD therapy. As an AP water-based formulation, BX quickly restores brain AP levels in late pregnancy. It affects a broader range of GABA_A receptors than benzodiazepines, which mainly target synaptic receptors. This comprehensive action helps restore neuronal signaling balance, which is crucial for optimal brain functioning. Clinical tests have shown BX's effectiveness in improving mood and related symptoms like anxiety and insomnia.

Zuruvae (zuranolone) and Its Significance in PPD Treatment. The introduction of zuranolone to the pharmaceutical scene marks a pivotal moment in PPD therapy. Zuranolone, designed to mimic AP, is a synthetic neurosteroid that overcomes the limitations of its natural counterpart, such as poor oral absorption and short half-life. With improved oral uptake and a longer half-life, zuranolone ensures a more stable presence in the system. These features make zuranolone advantageous, and taking it orally eliminates the challenges related to intravenous or frequent dosing, allowing patients to take their medication at home and giving them more control over their treatment. Promising results from Phase 3 trials indicate that zuranolone acts faster than traditional antidepressants, often taking longer to show benefits.

Furthermore, these positive effects last, suggesting its potential as a long-term solution for PPD. The FDA's recognition of zuranolone as a "breakthrough therapy" goes beyond acknowledging its effectiveness. It signals the drug's potential to revolutionize PPD treatment, providing a safe, powerful, and user-friendly treatment method.

Zuranolone's Clinical Role in PPD. The FDA's recent approval of zuranolone, the first oral medication for PPD, is a groundbreaking development. Evaluating this new drug's clinical significance requires understanding the robust evidence behind it. Clinical trials for zuranolone showed promising results, generating optimism among healthcare professionals and patients.

Key Findings from Clinical Research. A phase 3, double-blind, placebo-controlled clinical trial assessed zuranolone for treating PPD.

A total of 153 women with PPD were randomly assigned to either zuranolone 30 mg (77 women) or a placebo (76 women) to be taken daily for 14 days.

The main goal was to observe changes in the Hamilton rating scale for depression (The HAM-D-17, a widely used clinician-administered questionnaire designed to assess the severity of

depressive symptoms in individuals diagnosed with depression) by day 15.

On day 15, those taking zuranolone had a more significant improvement in HAM-D-17 scores than the placebo group.

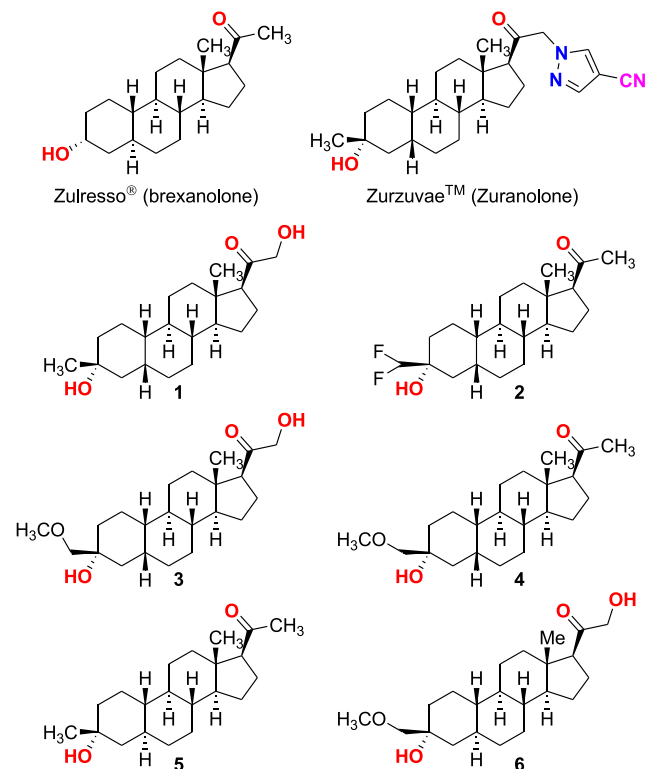
Improvements with zuranolone were evident from day 3 and lasted until day 45, including response and remission rates.

Other benefits of zuranolone over the placebo included improvements in the Montgomery–Asberg depression rating scale (MADRS, a 10-item clinician-administered scale that assesses the severity of depressive symptoms), the Hamilton anxiety rating scale (HAM-A or HARS, a 14-item clinician-administered scale assessing the severity of anxiety), and the clinical global impression-improvement (CGI-I, a 7-point scale that clinicians use to assess how much a patient's illness has improved or worsened relative to a baseline state).

Most participants tolerated zuranolone well with no withdrawal symptoms, although some reported side effects like sleepiness, headaches, and dizziness.

In summary, the study found that zuranolone offers rapid, meaningful, and lasting relief from depressive symptoms in women with PPD and has a good safety profile.

Key Structures.



Biological Assay. TBPS binding assays, HERG assay, and patch clamp cellular electrophysiology to measure in vitro potency and efficacy of GABA_A receptor modulators in Ltk cells.

Biological Data. The table below shows TBPS binding data for exemplary compounds and the effect of dosing conditions on zuranolone plasma pharmacokinetic (PK) parameters.

Compound		TBPS binding IC ₅₀ (nM)		
1		86		
2		33		
3		170		
4		41		
5		93		
6		94		
PK Parameters	Fed Capsules [high-fat meal]	Fasted Capsules		
C _{max} (ng/mL)	19 ^a	63.12	20 ^a	21.81
AUC _{0-t} (h*ng/mL)	19 ^a	837.55	20 ^a	529.62
AUC _{0-inf} (h*ng/mL)	5 ^a	1013.04	5 ^a	639.69

Recent Review Articles. See refs 1–6.

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Notes

The author declares no competing financial interest.

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